Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Remdesivir Reduces Mortality in Hemato-Oncology Patients with COVID-19

Bogusz Jan Aksak-Wąs[1], Daniel Chober[1], Karol Serwin[1], Kaja Scheibe[1], Jolanta Niścigorska-Olsen[2], Anna Niedźwiedź[3], Monika Dobrowolska[3], Katarzyna Żybul[4], Marta Kubacka[4], Agnieszka Zimoń[5], Ewa Hołda[4], Joanna Mieżyńska-Kurtycz[4], Marta Gryczman[6], Grzegorz Jamro[7], Paweł Szakoła[8], Miłosz Parczewski[1]

[1]Department of Infectious, Tropical Diseases and Immune Deficiency, Pomeranian Medical University in Szczecin, Szczecin, Poland; [2]Department of Infectious, Tropical Diseases and Immune Deficiency, Provincial Hospital, Szczecin, Poland; [3]Department of Diabetology and Internal Diseases, Provincial Hospital, Szczecin, Poland; [4]Department of Internal Medicine and Oncology, Provincial Hospital, Szczecin, Poland; [5]Department of Rheumatology, Department of Rehabilitation, Provincial Hospital, Szczecin, Poland; [6]Department of Nephrology and Kidney Transplantation, Dialysis Station, Provincial Hospital, Szczecin, Poland; [7]Department of Otolaryngology with the Sub-Department of Otolaryngology for Children, Provincial Hospital, Szczecin, Poland; [8]Department of General and Transplant Surgery, Department of Vascular Surgery, Provincial Hospital, Szczecin, Poland

Correspondence: Bogusz Jan Aksak-Wąs, Pomeranian Medical University, Department of Infectious, Tropical Diseases and Immune Deficiency, Arkońska 4, Szczecin, 71-455, Poland, Tel +48918139455, Fax +49918139449, Email bogusz.aw@gmail.com

Introduction: Remdesivir is the first agent with proven clinical efficacy against coronavirus disease 2019 (COVID-19); however, its benefit is associated with early use, and its efficacy has been poorly studied in patients with hemato-oncological diseases, who have an increased risk of a severe course of infection. This study aimed to assess the effects of remdesivir on mortality, mechanical ventilation, and the duration of hospitalization in both the general population and in patients with hemato-oncological diseases.

Materials and Methods: Longitudinal data for 4287 patients with confirmed COVID-19 were analyzed, including a subset of 200 individuals with hemato-oncological diseases. In total, 1285 (30.0%) patients received remdesivir, while the remaining patients were treated with other methods. Survival statistics for the 14- and 30-day observation time points were calculated using non-parametric and multivariate Cox models.

Results: Mortality for the 14- and 30-day observation time points was notably lower among patients receiving remdesivir (7.2% vs 11.6%, $p < 0.001$ and 12.7% vs 16.0, $p = 0.005$, respectively); however, in multivariate models adjusted for age, sex, lung involvement, and lactate dehydrogenase and interleukin-6 levels, the administration of remdesivir did not reduce patient mortality at either the 14-day or 30-day time points. Among patients with haemato-oncological disease, significant survival benefit was observed at 14 and 30 days for patients treated with remdesivir (11.3% vs.16.7% and 24.2% vs 26.1%, respectively; $p < 0.001$). A favorable effect of remdesivir was also noted for the 14-day time point in multivariate survival analysis (HR:4.03 [95% confidence interval:1.37–11.88]; $p = 0.01$).

Conclusion: Remdesivir significantly reduced the early mortality rate in COVID-19 patients with comorbid hemato-oncological disease, which emphasizes the need to administer this agent to immunosuppressed patients.

Keywords: COVID-19, SARS-COV-2, remdesivir, mortality, hemato-oncology

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China, with the subsequent rapid identification of pneumonia-associated coronavirus disease 2019 (COVID-19).[1,2] Since then, more than 454 million cases have been reported globally, and more than 6 million people have died from the disease (1.32% mortality). In Poland, more than 5.5 million cases have been reported, with a mortality rate of 1.95%.[3] The COVID-19 pandemic has affected almost all countries, but with divergent mortality rates across different patient populations.[4] Severe disease risk factors include older age (> 65 or 75 years according to some studies); male sex; black race; and the presence of chronic diseases, such as kidney disease, diabetes, obesity, hypertension, and asthma.[5] Active neoplastic disease is another risk factor for severe outcome in COVID-19 patients,[6] as well as hematological

Received: 13 June 2022
Accepted: 7 August 2022
Published: 25 August 2022

© 2022 Aksak-Wąs et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

malignancies and previous chemotherapy.[7,8] Studies have also shown that mortality may be affected by the initiation of disease-modifying drugs, such as tocilizumab and baricitinib.[9,10] Patients with immune deficiency have a significantly higher risk of a severe course of COVID-19 and, according to numerous observations, may have active replication of SARS-CoV-2 for prolonged periods. For this reason, direct antiviral therapy is important for immunodeficient individuals.[11] Data thus far indicate a poorer prognosis among patients with hematological diseases, but no data on the effect of antiviral treatment in this group have been published.

Since the beginning of the pandemic, intense research has been conducted to identify effective treatments for COVID-19. The first drug with antiviral properties to be used in patients infected with SARS-COV-2 was remdesivir (approved on 03/07/2020 by the European Commission, based on a positive opinion of the European Medicines Agency), which was repurposed from the treatment of Ebola virus disease.[12] Since then, two more agents with antiviral properties have been introduced, namely, the viral RNA polymerase inhibitor, molnupiravir, and the ritonavir-boosted protease inhibitor, nirmatrelvir.[13,14] The benefits of these agents are largely limited to the early stage of SARS-CoV-2 infection, during viral replication, but they have also been reported to be effective in case studies of immunodeficient patients with prolonged viral shedding.[15] Low-dose steroids (mainly dexamethasone), low-molecular-weight heparin, symptomatic drugs, and oxygen therapy remain the standard of care for patients with COVID-19.[16] However, COVID-19-associated mortality is largely associated with the later phase of the disease, including cytokine storm syndrome[17] and immune exhaustion.

Studies of the efficacy of remdesivir have been conducted since the beginning of the pandemic, with divergent results. In the seminal Adaptive COVID-19 Treatment Trial, remdesivir was shown to be superior to placebo at shortening the time to recovery in adults hospitalized with COVID-19 and with evidence of lower respiratory tract infection.[18] However, in the recent DisCoVeRy study, no clinical benefit of remdesivir was demonstrated in patients admitted to the hospital for COVID-19 and who required oxygen support and had symptoms lasting > 7 days.[19] In other studies, such as NCT04292899 and EUPAS34303, remdesivir has been shown to be associated with significantly greater recovery rates (74.4% of remdesivir-treated patients vs 59.0% of non-remdesivir-treated patients at day 14) and a 62% decrease in the odds of death compared with standard-of-care treatment in patients with severe COVID-19.[20] A real-world meta-analysis published by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium in 2021 that included 96,859 COVID-19 patients, showed that the patients who benefited most from the inclusion of remdesivir were those who did not use or were not currently using low-flow oxygen delivery systems. However, there was no evidence for an effect on mortality in any of the groups studied.[21]

In this study, we aimed to analyze the use of remdesivir and assess its impact on mortality, progression to invasive oxygen therapy, and duration of in-hospital treatment in a large cohort of COVID-19 patients. In this real-life study, we assessed the effectiveness of remdesivir treatment from the perspective of routine clinical care. The key analysis assessed the efficacy of remdesivir treatment among COVID-19 patients with concomitant hemato-oncological diseases. This group commonly receives immunosuppressive or long-term steroid treatment, resulting in prolonged SARS CoV-2 replication and shedding.[11]

Materials and Methods

Study Population

Longitudinal data were collected from 4287 COVID-19 patients followed up at the Department of Infectious Diseases, Pomeranian Medical University, Szczecin, Poland. The study protocol was approved by the Bioethical Committee of the Pomeranian Medical University (approval KB-0012/92/2020). Study complies with the Declaration of Helsinki. Informed consent for data analysis was obtained from all participants and the data were fully anonymized before statistical analyses. Patients participating in the study were observed from March 4, 2020 to January 23, 2022 when the database was closed. The first patient in our cohort was administered remdesivir in August 2020. The observation time was counted from the date of hospital admission to the date of discharge or death, and the total in-hospital treatment time was used in the analyses. All patients analyzed in this study had mild-to-moderate (requiring oxygen support only) or severe (requiring mechanical ventilation in the intensive care unit) COVID-19-related pneumonia and presented with clinical symptoms of cough, dyspnea, and/or fever (> 38 °C) and ≤ 94% oxygen saturation at admission. In every case,

a positive polymerase chain reaction test for SARS-CoV-2 was obtained from a pharyngeal swab, and pneumonia was confirmed using chest computed tomography (CT). The decision to introduce remdesivir was made by the physician based on the guidelines and recommendations of the Polish Association of Epidemiologists and Infectiologists[22–24] Within this dataset, we separately analyzed the treatment outcomes for patients with concomitant hematological or oncological diseases based on the codes listed in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

Clinical data, including age; sex; comorbidities based on the presence of a malignancy; treatment history; the duration of in-hospital stay; the duration of treatment in the intensive care unit; survival statistics; baseline blood oxygenation levels; chest CT scan results; and selected laboratory parameters, such as full blood count and serum procalcitonin, C-reactive protein, interleukin-6, lactate dehydrogenase, D-dimer, asparagine, alanine aminotransferase, gamma-glutamyl transpeptidase, total bilirubin, troponin, creatine kinase myocardial band, and glucose levels, were collected from the medical records. Renal creatinine levels were used to calculate glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula.

Parameters included in the Cox analysis were chosen according to their influence on the disease process, as determined in previous studies.[25,26] The included parameters were age; sex; percentage of lung inflammation; and laboratory values, such as those related to lung involvement (interleukin-6 and lactate dehydrogenase levels). Moreover, remdesivir treatment during the therapeutic process was the main prognostic factor.

As multiple studies have evaluated the effect of remdesivir on the course of infection and analyzed its effects at different endpoints[18,27,28] we decided to curate the data for the two most commonly used time points, namely 14 and 30 days. To identify factors influencing the risk of mechanical ventilation, the same variables that were included in the mortality analyses were used. The patients' characteristics according to hemato-oncological diagnoses are shown in Table 1.

Statistics

Mann–Whitney *U*-tests were used to compare non-parametric variables, while chi-square tests were used to compare nominal data between the analyzed groups. For normalization, the effect of the analyzed parameters on COVID-19-related mortality was censored at two time points previously associated with mortality.[18,20,21,29] Furthermore, for the overall hospitalization analysis, there were no observation endpoints implemented, and therefore, the Kaplan–Meier cumulative mortality rate was calculated using statistically significant survival data identified using the Log rank test. Unadjusted and multivariate Cox proportional hazards models were used to assess the effects of the analyzed parameters on the risk of death and to calculate hazard ratios (HRs). The best fit based on Akaike's information criterion was selected. Statistical significance was set at $p < 0.05$.

Results

General Population of SARS-COV-2-Infected Individuals

Patient Characteristics by Remdesivir Use

The study group had more men than women (n = 2405; 56.1%) and had a median age of 67 years (interquartile range [IQR]: 55–75 years). Patients who received remdesivir were significantly younger, with a median age of 63 (IQR: 51–72) years, compared to those who did not receive remdesivir, who had a median age of 68 (IQR: 57–77) years ($p < 0.001$). Differences in sex distribution were observed, with male patients being more commonly treated with remdesivir ($p = 0.003$). In general, inflammatory parameters were less pronounced in the remdesivir group, but lung involvement was similar between patients receiving and not receiving remdesivir (Table 2). Mortality rates were 16.7% (718 patients) in the total study population, 14.7% (189 patients) in the remdesivir group, and 17.6% (529 patients) in the non-remdesivir group; p=0,02.

Effect on Remdesivir Treatment on Mortality, Time to Mechanical Ventilation, and Duration of in-Hospital Treatment

At the 14-day observation time point, 93 (7.2%) patients who received remdesivir had died, compared to 347 (11.6%) who did not receive remdesivir ($p < 0.001$). In addition, the mortality rate was notably lower at the 30-day observation

Table 1 Patients' Characteristics Based on Their ICD-10 Diagnosis

Number of Patients	Disease Based on the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)
24 (10.8%)	Leukemia (myeloid, lymphoid)
8 (3.6%)	Lymphomas (Hodgkin's, non-Hodgkin's, follicular, non-follicular, and mature T/natural killer cell lymphomas)
5 (2.2%)	Multiple myeloma
8 (3.6%)	Malignant neoplasm of the nervous system
14 (6.3%)	Malignant neoplasm of the genitourinary system
8 (3.6%)	Malignant neoplasm of the breast
5 (2.2%)	Malignant neoplasm of the skin, bones, or other connective or soft tissue
22 (9.9%)	Malignant neoplasm of the respiratory tract
12 (5.4%)	Malignant neoplasm of the parenchymal organs of the abdominal cavity (liver, pancreas, or other)
19 (8.5%)	Malignant neoplasm of the digestive tract
3 (1.3%)	Sarcoidosis
4 (1.8%)	Myelodysplastic syndromes
3 (1.3%)	Immunodeficiency associated with different factors
1 (0.4%)	Diseases of the spleen
1 (0.4%)	Agranulocytosis
19 (8.5%)	Neoplasm of uncertain or unknown type
4 (1.8%)	Two or more neoplasms
61 (27.6%)	Other hematological diseases

time point in the remdesivir group (n = 163; 12.7%). than the non-remdesivir group (n = 481, 16.0%; p = 0.005). However, in multivariate Cox hazard analysis adjusted for age, sex, lung involvement and lactate dehydrogenase and interleukin-6 levels, it was found that the administration of remdesivir had no effect on the mortality of SARS-COV-2-infected individuals at 14 days, with an HR of 1.18 (95% CI: 0.93–1.49, p = 0.2), and 30 days, with an HR of 1.06 (95% CI: 0.88–1.28, p = 0.5). For patients who did not receive remdesivir, the factors influencing mortality for both time points were older age and higher interleukin-6 and lactate dehydrogenase levels. A higher percentage of lung involvement was important at the 30-day time point (Table 3).

Additionally, multivariate Cox models were used to analyze the risk of mechanical ventilation. The model adjusting for age, sex, percentage of lung involvement and interleukin-6 and lactate dehydrogenase levels indicated no difference in the risk of mechanical ventilation between SARS-COV-2-positive patients treated with or without remdesivir (HR: 0.88 [95% CI: 0.68–1.15], $p = 0.36$). Mechanical ventilation was required in 120 (9.3%) patients treated with remdesivir and 139 (4.6%) patients not treated with remdesivir. The only variable significantly associated with the risk of mechanical ventilation was a higher lactate dehydrogenase level (Table 4). Furthermore, there was no association between remdesivir treatment and the duration of in-hospital treatment (remdesivir group, median time: 11.7 [IQR: 8.5–16.8] days vs non-remdesivir group, median time: 12.0 [IQR: 8.1–16.8]; $p = 0.61$).

Table 2 Comparison of the Analyzed Cohorts in the General Database

Parameter	Remdesivir Group, Median (IQR)	Number of Patients	Non-Remdesivir Group, Median (IQR)	Number of Patients	*p* value
Age (years)	63 (51–72)	1270	68 (57–77)	2959	< 0.001
Gender	Female (519; 40.4%) Male (765; 59.6%)	1284	Female (1362; 45.4%) Male (1640; 54.6%)	3002	0.003
Percentage of lung involvement	13.7 (5.7–25.8)	1285	13.6 (4.9–27.7)	3002	0.56
WBC ($\times 10^3/\mu L$)	5.7 (4.4–7.5)	1285	7.1 (5.3–9.5)	2996	< 0.001
NEU ($\times 10^3/\mu L$)	4 (2.9–5.8)	1284	5.2 (3.5–7.4)	2995	< 0.001
LYM ($\times 10^3/\mu L$)	0.9 (0.7–1.3)	1283	1.1 (0.7–1.5)	2995	< 0.001
RBC ($\times 10^6/\mu L$)	4.7 (4.3–5.1)	1285	4.6 (4.1–5)	2996	< 0.001
HGB (g/dL)	14.1 (12.9–15)	1285	13.6 (12.2–14.8)	2996	< 0.001
HCT (%)	41 (37.8–43.6)	1285	39.7 (36.1–42.9)	2996	< 0.001
PLT ($\times 10^3/\mu L$)	185 (148–229)	1285	220 (167.5–286)	2996	< 0.001
PCT (ng/mL)	0.1 (0.1–0.2)	1269	0.1 (0.1–0.3)	2907	< 0.001
CRP (mg/L)	57.8 (24.9–113.8)	1285	64.8 (24.3–126.1)	2999	0.07
IL-6 (pg/mL_	48.3 (23.2–90.9)	1283	43.6 (18.3–94.4)	2964	0.02
LDH (U/L)	337 (258–454)	1232	329 (246–456)	2852	0.29
D-dimer (µg/L)	508 (292.5–961.8)	1284	714 (359–1758)	2913	< 0.001
eGFR CKD-EPI (mL/min/ 1.73 m^2)	78.3 (57.7–96.5)	1268	74 (48.8–94.8)	2955	< 0.001
AST (U/L)	40 (29–60)	1236	38 (18–58)	2885	0.002
ALT (U/L)	31 (22–48)	1235	31 (20–49)	2888	0.1
Serum glucose (mg/dL)	116 (103–141)	1215	118 (103–147)	2804	0.04
CK-MB (ng/mL)	1.4 (0.9–2.5)	1242	1.7 (1–3.1)	2851	< 0.001
Troponin (ng/L)	11.2 (6.4–20.2)	1221	15.3 (8.3–32.6)	2780	< 0.001
GGTP (U/L)	45 (26–79)	1200	45 (26–87)	2703	0.59
Total bilirubin (mg/dL)	0.4 (0.3–0.6)	1190	0.5 (0.3–0.7)	2667	< 0.001

Abbreviations: WBC, white blood cells; NEU, neutrophils; LYM- lymphocytes; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; PLT, platelets; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; eGFR CKD-EPI, glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; AST, asparagine aminotransferase; ALT, alanine aminotransferase; CK-MB- creatine kinase myocardial band; GGTP, gamma-glutamyl transpeptidase; IQR, interquartile range.

Hemato-Oncology Population of SARS-COV-2 Infected Individuals

Patient Characteristics

The characteristics of hemato-oncology patients were similar to those of the overall group, with a similar sex and age distribution (110 [55.0%] men; median age of 69 years [IQR: 61–75]). Patients who received remdesivir in this group were also significantly younger, with a median age of 65.5 (IQR: 58–74), than patients who did not receive remdesivir, who had a median age of 70 (IQR: 63–76 years (p = 0.05). Key differences in the laboratory parameters for the

Table 3 Mortality Analysis of Data from the General Database

14-Day Time Point								
	Effect	***p* value (Cox Hazard)**	**Hazard Ratio**	**95% CI, Lower**	**95% CI, Upper**	**Median (IQR) for Patients Who Died**	**Median (IQR) for Patients Who Survived**	***p* value (Mann Whitney-U)**
Age		< 0.001	1.073	1.063	1.083	78.0 (IQR: 69.0–86.0)	65.0 (IQR: 54.0–73.0)	< 0.001
Percent of lung involvement		< 0.001	1.037	1.032	1.042	33.7 (IQR: 16.4–51.5)	12.4 (IQR: 4.7–24.7)	< 0.001
Interleukin-6 level		< 0.001	1.0003	1.0002	1.0004	107.5 (IQR: 49.7–213.0) pg/mL	40.9 (IQR: 18.5–83.3) pg/mL	< 0.001
Lactate dehydrogenase level		< 0.001	1.001	1.0006	1.0013	477.5 (IQR: 332–604) U/L	322.0 (IQR: 244–433) U/L	< 0.001
Gender	Male	0.96	1.005	0.82	1.23			
Remdesivir	No	0.2	1.18	0.93	1.49			
30-day time point								
Age		< 0.001	1.063	1.056	1.072	75.0 (IQR: 68.0–84.0)	65.0 (IQR: 53.0–73.0)	< 0.001
Percent of lung involvement		< 0.001	1.034	1.034	1.038	32.7 (IQR: 15.9–51.5)	11.7 (IQR: 4.5–23.4)	< 0.001
Interleukin-6 level		< 0.001	1.0003	1.0002	1.0004	102.0 (IQR: 48.7–187.0) pg/mL	39.2 (IQR: 17.9–79.3) pg/mL	< 0.001
Lactate dehydrogenase level		< 0.001	1.0007	1.0004	1.001	464.0 (IQR: 327.0–599.0) U/L	318.0 (IQR: 241.0–425.0) U/L	0.005
Gender	Male	0.6	1.05	0.89	1.24			
Remdesivir	No	0.5	1.06	0.88	1.28			

Abbreviations: CI, confidence interval; IQR, interquartile range.

Table 4 Risk of Mechanical Ventilation at the 30-Day Time Point in the General Population

	Effect	*p* value (Multivariant Cox Hazard)	Hazard Ratio	95% CI, Lower	95% CI, Upper	Median (IQR) for Patients Requiring Mechanical Ventilation	Median (IQR) for Patients Who Survived	*p* value (Mann Whitney-U)
Age		0.31	1.01	0.99	1.03	66.0 (IQR: 61.0–72.0)	79.0 (IQR: 70.0–86.0)	< 0.001
Percentage of lung involvement		0.8	1.0	0.99	1.01	46.5 (IQR: 31.3–58.8)	26.5 (IQR: 11.8–47.0)	< 0.001
Interleukin-6 level		0.6	1.00009	0.9998	1.0004	103.0 (IQR: 58.7–165.0) pg/mL	97.9 (IQR: 44.3–194.0) pg/mL	0.77
Lactate dehydrogenase level		0.003	1.0012	1.0004	1.0019	557.0 (IQR: 417.5–737.5) U/L	428.0 (IQR: 298.0–556.0) U/L	< 0.001
Gender	Female	0.97	0.99	0.72	1.37			
Remdesivir	Yes	0.25	0.83	0.61	1.14			

Abbreviations: CI, confidence interval; IQR, interquartile range.

remdesivir group were lower neutrophil and platelet counts and D-dimer levels, but there were no notable differences in inflammatory parameters (Table 5). The mortality rates were 30.5% (61 patients) in the total group, 8.5% (17 patients) in the remdesivir group, and 22.0% (44 patients) in the non-remdesivir group ($p = 0.53$).

Effect on Mortality, Risk of Mechanical Ventilation, and in-Hospital Treatment Duration

For both observed time points, more patients died in the group without remdesivir usage. At the 14-day time point, 7 (11.3%) patients in the remdesivir group died compared to 23 (16.7%) in the non- remdesivir group ($p = 0.32$). At the 30-day time point, 15 (24.2%) patients in the remdesivir group died compared to 36 (26.1%) in the non-remdesivir group ($p = 0.78$).

In the multivariate Cox hazard analysis, administration of remdesivir was found to significantly reduce mortality in SARS-COV-2-infected patients during the 14-day observation period (HR: 4.03 [95% CI: 1.37–11.88; $p = 0.01$; Figure 1). This effect was not observed at the 30-day time point (HR: 1.44 [95% CI: 0.75–2.75; Table 6).

When the risk of mechanical ventilation was analyzed using multivariate models, two clinical factors remained significant. Younger patients (HR: 0.8 [95% CI: 0.7–1.0], $p = 0.006$) and women had a higher risk of mechanical ventilation (HR: 18.8 [95% CI: 2.1–165.2], $p = 0.008$). There were six women (6.7%) and 12 men (10.9%) who required mechanical ventilation. However, remdesivir treatment did not affect the time to mechanical ventilation (HR: 1.9 [95% CI: 0.5–6.7], $p = 0.28$). Other factors affecting the need for mechanical ventilation were a higher percentage of lung inflammation and higher interleukin-6 levels (Table 7).

Discussion

This study assessed the effect of remdesivir treatment on the severity of infection, mortality rate, and the risk of mechanical ventilation in COVID-19 patients. The analysis included a large group of more than 4.000 patients treated in a single center in Poland. This cohort was larger than the cohorts analyzed in other single-center studies and in many multicenter studies. It was almost 2.5 times larger than the largest Polish cohort, SARSTer[29] and almost 3.5 times larger than the Canadian-wide CATCO cohort.[30] The data analyzed in this study account for more than 4% of all analyzed data in the largest cohort assessed to date.[21]

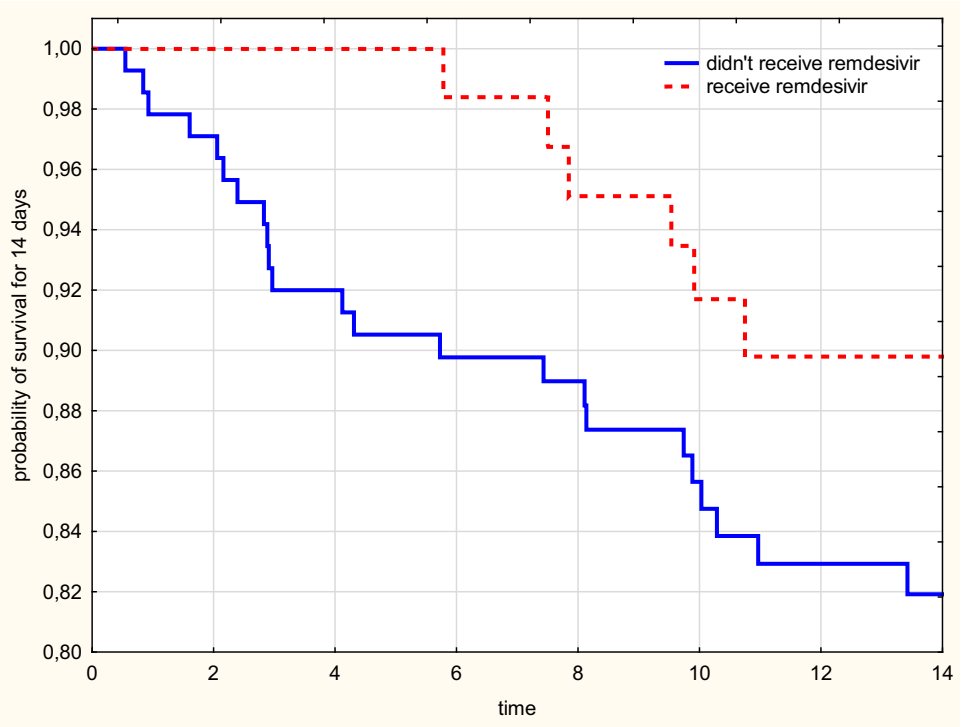
No overall positive effect of remdesivir treatment was demonstrated in this large cohort of hospitalized patients. However, in the group of patients with hemato-oncological comorbidity, a significant reduction in mortality was

Table 5 Comparison of the Analyzed Groups in the Hemato-Oncology Dataset

Parameter	Patients Who Received Remdesivir, Median (IQR)		Number of Patients	Patients Who did not Receive Remdesivir, Median (IQR)		Number of Patients	*p* value
Age (years)	65.5 (58–74)		62	70 (63–76)		138	0.05
Gender	Female (33; 53.2%)	Male (29; 46.8%)	62	Female (57; 41.3%)	Male (81; 58.7%)	138	0.1
Percentage of lung involvement	19.6 (5.3–26.1)		62	9.5 (2.1–29.3)		138	0.24
WBC ($\times 10^3/\mu L$)	6.4 (3.3–10.9)		62	7.9 (5.1–11.6)		137	0.054
NEU ($\times 10^3/\mu L$)	4.6 (2–7.6)		62	5.7 (3.5–8.1)		137	0.04
LYM ($\times 10^3/\mu L$)	0.8 (0.5–1.5)		61	0.9 (0.5–1.4)		137	0.85
RBC ($\times 10^6/\mu L$)	4.2 (3.4–4.6)		62	3.9 (3.1–4.5)		137	0.22
HGB (g/dL)	11.9 (9.7–13.8)		62	11.4 (9.1–13.1)		137	0.14
HCT (%)	35.3 (29.1–40.2)		62	33.9 (28.1–38.2)		137	0.22
PLT ($\times 10^3/\mu L$)	161.5 (103–203)		62	212 (137–293)		137	< 0.001
PCT (ng/mL)	0.1 (0.1–0.3)		62	0.2 (0.1–0.5)		135	0.25
CRP (mg/L)	57.9 (17.5–144.1)		62	73.8 (22–147.8)		138	0.41
IL-6 (pg/mL)	45.2 (18.6–119)		62	46.3 (18.5–113)		136	0.77
LDH (U/L)	367 (276–515)		61	315 (229–504)		131	0.14
D-dimer (µg/l)	792.5 (466–1632.1)		62	1308 (529.4–3512)		134	0.02
eGFR CKD-EPI (mL/min/ 1.73 m^2)	71.7 (50.2–95.2)		62	74.2 (45.3–93.2)		136	0.6
AST (U/L)	38 (27–62)		61	31 (24–58)		131	0.23
ALT (U/L)	36 (24–56)		61	27 (16–42)		131	0.02
Serum glucose (mg/dL)	116 (104–145)		57	114.5 (94–139)		126	0.63
CK-MB (ng/mL)	1.3 (0.8–1.9)		58	2 (1.3–3.7)		123	0.001
Troponin (ng/L)	15 (7.9–25.3)		59	23.5 (13.6–49.4)		121	0.001
GGTP (U/L)	66 (35–88)		59	55 (27–145)		120	0.77
Total bilirubin (mg/dL)	0.5 (0.3–0.7)		59	0.4 (0.3–0.6)		126	0.6

Abbreviations: WBC, white blood cells; NEU, neutrophils; LYM- lymphocytes; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; PLT, platelets; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; eGFR CKD-EPI, glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; AST, asparagine aminotransferase; ALT, alanine aminotransferase; CK-MB- creatine kinase myocardial band; GGTP, gamma-glutamyl transpeptidase; IQR, interquartile range.

demonstrated, with a four-fold lower risk of death than patients who did not receive remdesivir during the 14-day observation period. Patients who did not receive remdesivir were admitted to the hospital when the drug was not yet available, or were not eligible to receive it according to Polish recommendations (due to either contraindications or because they were already past the replication phase of infection). At the time of writing this manuscript, no other studies



Group sizes for the corresponding time points							
time point (days)	**0.55**	**3.61**	**6.69**	**9.76**	**12.83**	**14**	cumulative % of survival
received remdesivir	62	62	61	58	42	35	**89.8%**
didn't receive remdesivir	138	125	118	102	85	78	**81.9%**

Figure 1 Effect of remdesivir treatment on 14-day survival in the haemato-oncology group.

were found assessing the effect of remdesivir specifically in a group of hemato-oncological patients, which indicates the novelty of this real-life observational dataset.

Other groups of patients who showed a beneficial effect of remdesivir on survival were patients with atrial fibrillation.[31] However, in some cases, for example in patients with sepsis, the implementation of remdesivir may not have a beneficial therapeutic effect.[32]

In previous studies, the effect of remdesivir on patient survival has varied depending on the analyses performed. However, similar to our findings, the large CHARGE meta-analysis found no effect of remdesivir on mortality.[21] However, in that analysis, hemato-oncological patients were not specifically analyzed. Most studies have shown no effect of remdesivir on the requirement for mechanical ventilation. We also found no effect of remdesivir treatment on the risk of progression to more severe stages of disease requiring mechanical ventilation.[33] Consensus regarding the observation time for remdesivir-dependent survival is not easy to find, and many studies have analyzed multiple endpoints, including 10, 14, 15, 28, or 29 days.[18,21,29] In this study, we chose 14 and 28 days as the time points for in-hospital observation.

The current study showed associations between an array of laboratory and clinical variables and the severity of the course of SARS-COV-2 infection, including links between the levels of C-reactive protein, interleukin 6, and lactate dehydrogenase levels and glomerular filtration and COVID-19-related mortality. These data are similar to those from previously published studies.[25,26,34] The severity of lung tissue involvement was also associated with the severity of infection and increased mortality, which is consistent with the results of previous studies.[34]

Table 6 Analysis of Data from the Hemato-Oncology Database

14-Day Time Point								
	Effect	***p* value (Cox Hazard)**	**Hazard Ratio**	**95% CI, Lower**	**95% CI, Upper**	**Median (IQR) for Patients Who Died**	**Median (IQR) For Patients Who Survived**	***p* value (Mann Whitney-U)**
Age		0.03	1.047	1.004	1.094	73.5 (68.0–81.0)	68.0 (59.5–75.0)	0.009
Percentage of lung involvement		< 0.001	1.027	1.011	1.044	32.5 (IQR: 9.1–56.3)	9.8 (IQR: 2.3–25.5)	0.01
Interleukin-6 level		< 0.001	1.005	1.003	1.007	168.0 (IQR: 54.9–525.0) pg/mL	37.2 (IQR: 17.9–92.4) pg/mL	< 0.001
Lactate dehydrogenase level		0.01	1.0013	1.0003	1.0023	502.5 (IQR: 327.0–658.0) U/L	311.0 (IQR: 239.0–478.0) U/L	< 0.001
Gender	Male	0.09	0.46	0.19	1.13			
Remdesivir	No	0.01	4.03	1.37	11.88			
30-day time point								
Age		0.1	1.027	0.995	1.06	70.0 (65.0–76.0)	69.0 (60.0–75.0)	0.2
Percent of lung involvement		< 0.001	1.027	1.015	1.039	35.6 (IQR: 9.1–56.4)	9.1 (IQR:1.7–23.4)	< 0.001
Interleukin-6 level		< 0.001	1.0025	1.0012	1.0038	111.5 (IQR: 39.1–251.0) pg/mL	34.6 (17.2–87.7) pg/mL	0.002
Lactate dehydrogenase level		0.2	1.0007	0.9997	1.0016	454.0 (323.0–641.0)	295.0 (233.0–443.0)	< 0.001
Gender	Male	0.5	0.81	0.42	1.54			
Remdesivir	No	0.3	1.44	0.75	2.75			

Abbreviations: CI, confidence interval; IQR, interquartile range.

Table 7 Risk of Mechanical Ventilation at the 30-Day Time Point in Hemato-Oncology Patients

	Effect	*p* value (Multivariant Cox Hazard)	Hazard Ratio	95% CI, Lower	95% CI, Upper	Median (IQR) for Patients Requiring Mechanical Ventilation	Median (IQR) for Patients Who Survived	p value (U-Mann Whitney)
Age		0.01	0.84	0.74	0.95	63.0 (IQR: 57.0–69.0)	70,0 (IQR: 63.0–76.0)	0.007
Percentage of lung involvement		0.04	1.03	1.0	1.07	48.0 (IQR: 21.5–59.7)	9,7 (IQR: 2.2–26,5)	< 0.001
Interleukin-6 level		0.01	1.005	1.001	1.01	111.0 (IQR: 39.0–252.0) pg/mL	42.6 (IQR: 18.6–99.6) pg/mL	0.02
Lactate dehydrogenase level		0.6	1.001	0.997	1.006	477.0 (IQR: 360.0–584.0) U/L	310.0 (IQR: 235.0–497.0) U/L	0.001
Gender	Female	0.01	18.8	2.14	165.2			
Remdesivir	Yes	0.3	0.53	0.15	1.84			

Abbreviations: CI, confidence interval; IQR, interquartile range.

In the analyzed cohort, only lactate dehydrogenase levels were significantly associated with the requirement for mechanical ventilation in COVID-19 patients, which is consistent with previous data on the effects of selected laboratory parameters on the severity of infection.[25,26] The aforementioned reports regarding the effect of remdesivir treatment on mortality and mechanical ventilation are very ambiguous, while large meta-analyses have often indicated either a complete lack of an effect of remdesivir on the aforementioned parameters or shown discrepancies in the results.[21,33]

A significant reduction in mortality was observed in hemato-oncology patients who received remdesivir. These patients, according to the guidelines of the Polish Society of Epidemiologists and Doctors of Infectious Diseases, received remdesivir for a maximum of 10 days, whereas the general population receive remdesivir initially for 5 days, and then for 3 days if pneumonia is not observed. It has been shown that patients with immunodeficiency may harbor actively replicating SARS-CoV-2 virions for a long time, in some cases up to approximately 3 months.[35,36] These patients are particularly susceptible to severe courses of infection, including acute respiratory distress syndrome.[15,37,38] No data on mortality or mechanical ventilation risk in hemato-oncological patients were found from other cohorts. The effect of remdesivir on mortality in the general population is uncertain. While some studies have shown that it is effective at reducing mortality,[39] most of the data do not support its effect.[33,40] Moreover, there is a lack of data on the efficacy of remdesivir in hemato-oncology patients.

In addition to the aforementioned associations, a significant increase in both mortality and the risk of mechanical ventilation was demonstrated in women compared to men in the hemato-oncology patient group. These findings have not been confirmed in previous studies, which have shown an increased risk of severe infection in men, related to the influence of androgens on the severity of SARS-COV-2 infection.[41,42] Other analyzes have shown an adverse effect of female sex in younger COVID-19 patients,[43] therefore, these sex-specific differences may be due to local group characteristics.

Remdesivir seems to be effective in selected groups of patients, especially those with immunodeficiency, who are prone to prolonged viral shedding and severe disease. Meta-analyses in most cases have not confirmed the effects of remdesivir on the course of infection. Some have reported faster recovery in patients treated with remdesivir, but most have shown no effect on mortality.

Conclusions

Remdesivir significantly reduced the mortality rate in immunodeficient patients and significantly improved their prognosis, it may also have a beneficial effect when analyzing the general population. Further analyses of hemato-oncology patients and other patients with immune deficiencies are required, as these patients often require several lines of antireplication and anti-inflammatory treatment. Immunodeficient patients often require a very individualized approach, and after the end of the COVID-19 pandemic, they may be the group that continues to be most affected by this disease.

Study Limitations

This study has several limitations that should be noted. First, the cohort analyzed in this study was 100% Caucasian. Therefore, the study findings may not be applicable to other ethnic groups. Second, not all factors were collected for evaluation at baseline, as the type of tests performed depended on the decision of the attending physician and this may have affected their availability for statistical analysis. Third, this was a retrospective study in which all patients admitted to the study center were assessed. The decision to initiate treatment with remdesivir and other therapies, including anti-inflammatory and maintenance treatments, was entirely up to the treating physician of the patient. Moreover, the Polish Society of Epidemiologists and Doctors of Infectious Diseases guidelines were followed, and these guidelines changed during the pandemic. However, the study cohort included more than 4000 patients, and therefore, any missing data should not have greatly affected the overall results of the statistical analyses. As in other retrospective studies, this analysis assessed remdesivir in the context of standard care and different comorbidities and patient burdens. Such a broad analysis should adequately show the observed real-life dependencies.

Funding

The study was funded by the National Centre for Research and Development, Agreement No. SZPITALE-JEDNOIMIENNE/27/2020, 20 November 2020, for implementation and financing of a non-competitive project (Prevention and Treatment: COVID-19), titled "Development of Modern Laboratory Technologies, IT and Bioinformatics Dedicated to the Diagnosis and Prevention of SARS-CoV-2 Infections", implemented as part of the "Support for Homonymous Hospitals in Combating the Spread of SARS-CoV-2 Infection and Treating COVID-19" project.

Disclosure

Professor Miłosz Parczewski reports grants from National Centre for Scientific Research, during the conduct of the study. The authors declare no other conflicts of interests.

References

1. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020 [Internet]. [cited March 12, 2022]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-The-media-briefing-on-2019-ncov-on-11-february-2020. Accessed August 18, 2022.
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021;19(3):141–154. doi:10.1038/s41579-020-00459-7.
3. Flisiak R, Rzymski P, Zarębska-Michaluk D, et al. Demographic and clinical overview of hospitalized COVID-19 patients during the first 17 months of the pandemic in Poland. *J Clin Med*. 2021;11(1):117. doi:10.3390/jcm11010117
4. ArcGIS Dashboards [Internet]; [cited March 12, 2022]. Available from: https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf. Accessed August 18, 2022.
5. Ko JY, Danielson ML, Town M, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization: COVID-19-Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. *Clin Infect Dis*. 2021;72(11):E695–703. doi:10.1093/cid/ciaa1419
6. Booth A, Reed AB, Ponzo S, et al. Population risk factors for severe disease and mortality in COVID-19: a global systematic review and meta-analysis. *PLoS One*. 2021;16(3):e0247461. doi:10.1371/journal.pone.0247461
7. Tsukada N, Inamura J, Igarashi S, Sato K. 血液悪性疾患患者におけるCOVID-19院内発症例の重症化リスクの検討[A retrospective analysis of risk factors for severity of nosocomial COVID-19 in patients with hematological malignancy]. *Rinsho Ketsueki*. 2021;62(10):1474–1481. [Japanese]. doi:10.11406/rinketsu.62.1474.

8. Passamonti F, Cattaneo C, Arcaini L, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol*. 2020;7(10):e737–45. doi:10.1016/S2352-3026(20)30251-9
9. Chober D, Aksak W, Bobrek-Lesiakowska K, et al. Effectiveness of tocilizumab in patients with severe or critical lung involvement in COVID-19: a retrospective study. *J Clin Med*. 2022;11(9):2286. doi:10.3390/jcm11092286
10. Chober D, Aksak-Wąs B, Niścigorska-Olsen J, Niekrasz M, Parczewski M. Tocilizumab Use among Patients Who Developed Pulmonary Embolism in the Course of Cytokine Release Storm and COVID-19 Pneumonia—A Retrospective Study. *Biomedicines*. 2022;10(7):1581. doi:10.3390/biomedicines10071581
11. Helleberg M, Niemann CU, Moestrup KS, et al. Persistent COVID-19 in an immunocompromised patient temporarily responsive to two courses of remdesivir therapy. *J Infect Dis*. 2020;222(7):1103–1107. doi:10.1093/infdis/jiaa446
12. Mulangu S, Dodd LE, Davey RT. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293–2303. doi:10.1056/NEJMoa1910993.
13. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med*. 2022;386(15):1397–1408. doi:10.1056/NEJMoa2118542
14. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509–520. doi:10.1056/NEJMoa2116044
15. Nakajima Y, Ogai A, Furukawa K, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. *J Infect Chemother*. 2021;27(2):387–389. doi:10.1016/j.jiac.2020.12.001
16. Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: an overview. *Eur J Pharmacol*. 2020:889. Available from:, https://pubmed.ncbi.nlm.nih.gov/33053381/.
17. Chen LYC, Quach TTT. COVID-19 cytokine storm syndrome: a threshold concept. *Lancet Microbe*. 2021;2(2):e49–50. doi:10.1016/S2666-5247(20)30223-8.
18. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final Report. *N Engl J Med*. 2020;383(19):1813–1826. doi:10.1056/NEJMoa2007764
19. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209–221. doi:10.1016/S1473-3099(21)00485-0
20. Olender SA, Perez KK, Go AS, et al. Remdesivir for severe Coronavirus disease 2019 (COVID-19) versus a cohort receiving standard of care. *Clin Infect Dis*. 2021;73(11):E4166–74. doi:10.1093/cid/ciaa1041
21. Garibaldi BT, Wang K, Robinson ML, et al. Real-world effectiveness of remdesivir in adults hospitalized with Coronavirus disease 2019 (COVID-19): a retrospective, multicenter comparative effectiveness study. *Clin Infect Dis*. 2021; doi:10.1093/cid/ciab1035/6463010.
22. Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish association of epidemiologists and infectiologists as of March 31, 2020. *Pol Arch Intern Med*. 2020;130(4):352–357. doi:10.20452/pamw.15270
23. Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish association of epidemiologists and infectiologists. Annex no. 1 as of June 8, 2020. *Pol Arch Intern Med*. 2020;130(6):557–558. doi:10.20452/pamw.15424
24. Flisiak R, Parczewski M, Horban A, et al. Management of SARS-CoV-2 infection: recommendations of the Polish association of epidemiologists and infectiologists. Annex no. 2 as of October 13, 2020. *Pol Arch Intern Med*. 2020;130(10):915–918. doi:10.20452/pamw.15658
25. Ramasamy S, Subbian S. Critical determinants of cytokine storm and type I interferon response in COVID-19 pathogenesis. *Clin Microbiol Rev*. 2021;34(3):51.
26. Qu J, Sumali B, Lee H, et al. Finding of the factors affecting the severity of COVID-19 based on mathematical models. *Sci Rep*. 2021;11(1):. doi:10.1038/s41598-021-03632-x
27. Rezagholizadeh A, Khiali S, Sarbakhsh P, Entezari-Maleki T. Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. *Eur J Pharmacol*. 2021:897. Available from: https://pubmed.ncbi.nlm.nih.gov/33549577/.
28. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2021;384(9):795–807. doi:10.1056/NEJMoa2031994
29. Flisiak R, Zarębska-Michaluk D, Berkan-Kawińska A, et al. Remdesivir-based therapy improved the recovery of patients with COVID-19 in the multicenter, real-world SARSTer study. *Pol Arch Intern Med*. 2021;131(1):103–110. doi:10.20452/pamw.15735
30. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;194(7):E242–51. doi:10.1503/cmaj.211698
31. Bistrovic P, Manola S, Papic I, Jordan A, Ortner Hadziabdic M, Lucijanic M. Atrial fibrillation in COVID-19 patients receiving remdesivir, matched case-control analysis. *Am J Emerg Med*. 2022;59:182–183. doi:10.1016/j.ajem.2022.04.051
32. Lucijanic M, Cikara T, Bistrovic P, et al. Remdesivir use in COVID-19 patients might predispose bacteremia, matched case-control analysis. *J Infect*. 2022;85(2):174–211. doi:10.1016/j.jinf.2022.04.045
33. Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020;3:370.
34. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K. Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. *Physiology*. 2020;35(5):288. doi:10.1152/physiol.00019.2020
35. Goubet AG, Dubuisson A, Geraud A, et al. Prolonged SARS-CoV-2 RNA virus shedding and lymphopenia are hallmarks of COVID-19 in cancer patients with poor prognosis. *Cell Death Differ*. 2021;28(12):3297–3315. doi:10.1038/s41418-021-00817-9
36. Altamirano-Molina M, Pacheco-Modesto I, Amado-Tineo J. Prolonged viral shedding of SARS-CoV-2 in patients with acute leukemia. *Hematol Transfus Cell Ther*. 2022;44(2):299–300. doi:10.1016/j.htct.2021.11.017.
37. Avanzato VA, Matson MJ, Seifert SN, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. *Cell*. 2020;183(7):1901–1912.e9. doi:10.1016/j.cell.2020.10.049
38. Baang JH, Smith C, Mirabelli C, et al. Prolonged severe acute respiratory syndrome coronavirus 2 replication in an immunocompromised patient. *J Infect Dis*. 2021;223(1):23–27. doi:10.1093/infdis/jiaa666
39. Diaz GA, Christensen AB, Pusch T, et al. Remdesivir and mortality in patients with COVID-19. *Clin Infect Dis*. 2021; Available from https://pubmed.ncbi.nlm.nih.gov/34409431/.

40. Ansems K, Grundeis F, Dahms K, et al. Remdesivir for the treatment of COVID-19. *Cochrane Database Syst Rev*. 2021;8(8) doi:10.1002/14651858.CD014962
41. Mohamed MS, Moulin TC, Schiöth HB. Sex differences in COVID-19: the role of androgens in disease severity and progression. *Endocrine*. 2021;71(1):3. doi:10.1007/s12020-020-02536-6
42. Samadizadeh S, Masoudi M, Rastegar M, Salimi V, Shahbaz MB, Tahamtan A. COVID-19: why does disease severity vary among individuals? *Respir Med*. 2021;180:106356. doi:10.1016/j.rmed.2021.106356
43. Živković NP, Lucijanić M, Bušić N, et al. The associations of age, sex, and comorbidities with survival of hospitalized patients with coronavirus disease 2019: data from 4014 patients from a tertiary-center registry. *Croat Med J*. 2022;63(1):36–43. doi:10.3325/cmj.2022.63.36

Journal of Inflammation Research Dovepress

Publish your work in this journal

The Journal of Inflammation Research is an international, peer-reviewed open-access journal that welcomes laboratory and clinical findings on the molecular basis, cell biology and pharmacology of inflammation including original research, reviews, symposium reports, hypothesis formation and commentaries on: acute/chronic inflammation; mediators of inflammation; cellular processes; molecular mechanisms; pharmacology and novel anti-inflammatory drugs; clinical conditions involving inflammation. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/journal-of-inflammation-research-journal